Original Contributions

Clinically Recognized Dysplastic Nevi

A Central Risk Factor for Cutaneous Melanoma

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Objective.—To investigate the relationship of number and type of nevi to the development of melanoma.

Design.—Case-control study.

Setting.—Outpatient clinics in referral hospitals.

Patients.—Cases were 716 consecutive patients with newly diagnosed melanoma identified at 2 melanoma centers between January 1, 1991, and December 31, 1992. Stratified random sampling of patients from outpatient clinics was used to identify 1014 participating controls of the same age, sex, race, and geographic distribution as the melanoma cases. All study subjects underwent an interview, a complete skin examination, photography of the most atypical nevi, and, if the patient was willing, a biopsy of the most atypical nevus.

Main Outcome Measures.—Number and type of nevi on the entire body were systematically reported. All diagnoses of clinically dysplastic nevi were confirmed by expert examiners.

Results.—Risk for melanoma was strongly related to number of small nevi, large nondysplastic nevi, and clinically dysplastic nevi. In the absence of dysplastic nevi, increased numbers of small nevi were associated with an approximately 2-fold risk, and increased numbers of both small and large nondysplastic nevi were associated with a 4-fold risk. One clinically dysplastic nevus was associated with a 2-fold risk (95% confidence interval, 1.4-3.6), while 10 or more conferred a 12-fold increased risk (95% confidence interval, 4.4-31). Congenital nevi were not associated with increased risk of melanoma.

Conclusions.—Although nondysplastic nevi confer a small risk, clinically dysplastic nevi confer substantial risk for melanoma. On the basis of nevus number and type, clinicians can identify a population at high risk of this epidemic cancer for screening and intervention.

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DYSPLASTIC NEVI were first described in melanoma-prone families.[1-3] The role of these nevi in the development and histogenesis of melanoma has been evaluated subsequently in numerous clinical, epidemiologic, and histologic studies.[4-17] Although controversy remains regarding the clinical and histologic diagnoses of dysplastic nevi,[18,19] epidemiologic studies have consistently demonstrated substantial risk of melanoma associated with dysplastic nevi.[4-17] Few investigations have included enough subjects with total nevus counts to adequately assess the relative contribution of the number of dysplastic nevi and other nevi to melanoma risk. Two studies that have attempted to distinguish the effects of dysplastic and other nevi in melanoma risk have yielded conflicting results.[9,10] We undertook this multicenter case-control study to evaluate the risk of melanoma according to number and type of nevi.

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METHODS

The detailed project proposal was approved by the institutional review boards of the National Cancer Institute, Bethesda, Md; Westat Inc, Rockville, Md; University of California, San Francisco; and University of Pennsylvania, Philadelphia.

Identification of Subjects With Melanoma

Eligible subjects included all patients aged 20 to 79 years, with newly diagnosed invasive cutaneous melanoma between January 1, 1991, and December 31, 1992, examined at the Pigmented Lesion Clinic of the Hospital of the University of Pennsylvania or the Melanoma Clinic of the University of California, San Francisco. Patients were enrolled in the study at their initial evaluation related to the index melanoma. All diagnoses of index melanomas were confirmed by histologic review. Of 768 eligible subjects with melanomas, 30 refused participation in the study, but they did not differ in demographic characteristics from participants. Data were available for analysis for 738 melanoma cases (96%) (Table 1), 99% of whom were white.

Identification of Control Subjects

Controls were recruited from 12 clinics (including ambulatory care, internal medicine, endocrinology, cardiology, and otolaryngology) with catchment areas similar to the melanoma clinics at University of California, San Francisco, and University of Pennsylvania. Initial complaints of

the eligible controls varied widely: 40% were seen for routine physical examinations, 20% for cardiovascular examinations, 10% for infections, and 30% for other reasons. Patients with initial complaints of dermatologic or psychiatric problems were excluded. We used a stratified random sampling scheme to obtain control patients of the same age, race, sex, and geographic distribution as the melanoma patients. Of 1228 eligible control subjects, 193 refused participation; 5 had limited participation. They did not differ in demographic characteristics from participants. Data were available for analysis for 1030 controls (84%) (Table 1), 97% of whom were white.

Table 1.—Demographic Characteristics of Participating Cases and Controls

	No. (%)*	
	Cases	Controls
Sex		
Male	406 (55)	558 (54)
Female	330 (45)	466 (46)
Age, y		
20-29	54 (7)	96 (9)
30-39	136 (18)	202 (20)
40-49	205 (28)	234 (23)
50-59	125 (17)	205 (20)
60-69	138 (19)	167 (16)
70-79	78 (11)	120 (12)
Residence		
City	64 (8)	107 (10)
Adjacent counties	409 (56)	648 (63)
Beyond	265 (36)	275 (27)

*Some demographic data were missing for 2 cases and 6 controls.

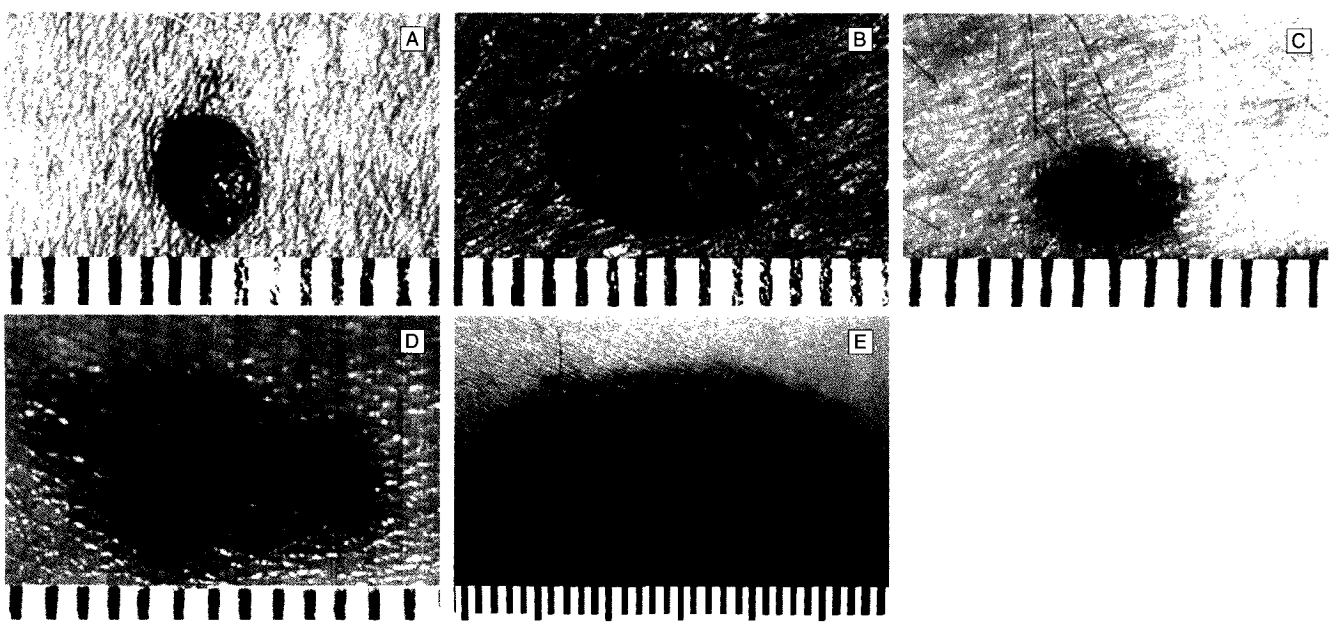
Data Collection

After obtaining informed consent, staff interviewed subjects in person. Interviews lasted 20 to 45 minutes and elicited subjects' history of sun exposure, occupation, residence, personal medical history, and family history of melanoma and other cancers. Staff examined the skin, counting all nevi larger than 2 mm over the entire skin surface (except for the scalp, pubic region, and perineum) in 3 size categories (≥8 mm, ≥5 mm and <8 mm, and <5 mm) and classifying them as clinically dysplastic or not. Nevus counts were based on the clinical examination only. Obligatory criteria for diagnosis of clinically dysplastic nevi were size of 5 mm or larger and flatness (entirely flat or having a flat component). At least 2 of the following were also necessary: variable pigmentation; irregular, asymmetric outline; and indistinct borders. All other nevi were considered nondysplastic for the nevus counts (Figure).

Other skin characteristics were recorded systematically, including number of nevus excision scars, freckling pattern, skin color, solar damage, and presence and size of congenital-type nevi. A nevus was considered to be a congenital-type nevus if it had been present since birth or shortly thereafter, was elevated, had stippled or uniform pigmentation, and had discrete borders. We attempted to acquire representative slides for all previous nevus biopsies, which were reviewed by the study pathologists (W.H.C., D.E.E., R.W.S.). We offered each person a biopsy of their most atypical nevus (even if the most unusual nevus was ordinary). Fifty-eight percent of cases and 90% of control subjects declined. Results of these optional biopsies were not used in this analysis.

Each study subject underwent photography of the entire back and of the 3 most atypical pigmented lesions. All nevus photographs were reviewed by senior expert examiners blind to the status of study subjects and to the original diagnoses of lesions by the recording examiner.[20] Pairwise agreement among expert clinicians occurred on average 87% of the time. Lesions not agreed on by examiners were not counted as clinically dysplastic nevi, but were deemed indeterminate. Dysplastic nevus status for each study subject was confirmed by an expert examiner.

A study subject was considered to have no dysplastic nevi if there were no clinically dysplastic nevi on the skin examination, no nevus biopsy specimens showing evidence of dysplasia, and no evidence of a precursor dysplastic nevus in the primary melanoma.[21] Subjects who lacked clinical dysplastic nevi, but who had histologic evidence of dysplastic nevi from previous excisions, were considered as a separate category in the logistic regressions to minimize misclassification in the referent group. Study subjects were therefore classified as having no dysplastic nevi, only histologic evidence without clinical evidence of dysplastic nevi, indeterminate



A, Small, ordinary nevus that is completed raised and symmetric in outline, with discrete borders. B, Large nondysplastic nevus that is completely raised and uniform in pigmentation, with a symmetric outline and distinct borders. The dark areas are keratin plugs. C, Small, flat nevus with asymmetric outline, variable pigmentation, and indistinct borders. This lesion has all the morphologic features of a clinically dysplastic nevus but does not meet the size criterion of greater than or equal to 5 mm. D, Clinically dysplastic nevus. The lesion is flat and large, almost 12 mm in largest diameter, irregular and asymmetric in outline, with indistinct borders, and color ranging from light tan to dark brown. E, A congenital nevus. The lesion is large, completely elevated, with discrete borders and stippled pigmentation.

Table 2.—Characteristics of the Index Melanomas

	No. (%)		
	Philadelphia, Pa	San Francisco, Calif	Total
Site			
Back	99 (26)	97 (27)	196 (27)
Arms	76 (20)	61 (17)	137 (19)
Legs	68 (18)	77 (21)	145 (20)
Other trunk	82 (22)	71 (19)	153 (21)
Head and neck	49 (13)	58 (16)	107 (13)
Thickness, mm			
<0.76	163 (44)	110 (31)	273 (37)
0.76-1.5	87 (23)	100 (28)	187 (26)
1.5-3.0	80 (21)	81 (22)	161 (22)
>3.0	43 (12)	67 (19)	110 (15)
Level of invasion			
2	114 (31)	85 (23)	199 (27)
3	125 (33)	144 (40)	269 (36)
4	111 (30)	98 (27)	209 (28)
5	16 (4)	17 (5)	33 (4)
Unclassified	8 (2)	20 (5)	28 (4)

Table 3.—Adjusted Estimated Relative Risks of Melanoma by Nevus Type and Number

No. of Nevi by Type	No. of Cases	No. of Controls	Adjusted* RR	Adjusted† RR	Adjusted‡ RR (95% CI)
Nevi >2 mm and <5 mm					
0-24	258	658	1.0	1.0	1.0 . . .
25-49	163	190	2.4	1.6	1.8 (1.3-2.5)
50-99	169	107	4.5	2.5	3.0 (2.1-4.4)
≥100	123	43	8.5	3.1	3.4 (2.0-5.7)
Nondysplastic nevi >5 mm					
0	239	507	1.0	1.0	1.0 . . .
1	135	224	1.3	1.0	0.9 (0.7-1.3)
2-4	188	195	2.0	1.4	1.3 (1.0-1.8)
5-9	86	51	3.7	1.9	1.7 (1.0-2.7)
≥10	65	21	7.2	2.3	2.3 (1.2-4.3)
Congenital nevi					
None	605	881	1.0	1.0	1.0 . . .
Solitary	74	85	1.3	1.1	1.1 (0.7-1.7)
Multiple	34	32	1.6	1.1	1.3 (0.7-2.5)
Dysplastic nevi§					
None	301	778	1.0	1.0	1.0 . . .
Indeterminate	72	127	1.5	1.1	1.0 (0.7-1.6)
1	64	50	3.8	2.2	2.3 (1.4-3.6)
2-4	121	33	11	6.9	7.3 (4.6-12)
5-9	45	15	8.6	4.4	4.9 (2.5-9.8)
≥10	55	6	32	12	12 (4.4-31)

*Adjusted for age, sex, center, and referral pattern. RR indicates relative risk.

†Mutually adjusted and adjusted for age, sex, center, referral pattern, and morphologic dysplastic nevi smaller than 5 mm.

‡Mutually adjusted and adjusted for age, sex, center, referral pattern, morphologic dysplastic nevi smaller than 5 mm, sunburns, freckles, solar damage, scars, nevus excisions, and family history of melanoma. CI indicates confidence interval.

§Not shown are those with no clinical evidence of dysplastic nevi, but histologic evidence on previous nevus biopsy (n=69).

if they had lesions not agreed on by examiners, or verified clinically determined dysplastic nevi. For those with clinically verified dysplastic nevi, the count on the clinical examination was used as the number of dysplastic nevi in all analyses.

Statistical Analyses

Relative risks (RRs) were estimated by the odds ratio with 95% confidence intervals (CIs), and tests for trend for univariate analyses of risk factors were estimated with the personal computer version of EPITOME.[22] The BMDP logistic regression models controlled simultaneously for numerous potential confounding variables.[23] To assess trend, variables were entered into models as 1-*df* scored variables. Subjects with unknown values for any variable in the multivariate analyses were excluded unless the unknown values were incorporated as a separate category in the variable.

RESULTS

Site distributions of the melanomas that established case eligibility were similar at the 2 study centers (Table 2), although the melanomas in Philadelphia tended to be somewhat thinner than those in San Francisco. Among participating study subjects, 22 cases and 10 controls had previously had another melanoma. These were excluded from the analyses to evaluate the risk of first primary melanoma.

The risk of melanoma related strongly to the number of small, large nondysplastic, and clinically dysplastic nevi (Table 3). There was no relationship between number or type of nevi and thickness or stage of melanoma. When mutually adjusted, RR estimates for each type of nevi decreased substantially, since number and type of nevi were strongly correlated. There was also a significant 2.6-fold (95% CI, 1.8-3.8) risk associated with nevi smaller than 5 mm that had the morphologic characteristics of dysplastic nevi on photography review but did not meet the size criterion to be included as dysplastic nevi. This variable was therefore included in all analyses adjusted for nevi. Further adjustment for important sun exposure variables (sunburns at an early age, total number of blistering sunburns, freckles, extent of actinic damage) did not substantially change the risks associated with small, large, or dysplastic nevi (Table 3). In a similar manner, adjustment for other host characteristics, such as family history of melanoma, skin color, ability to tan, or eye or hair color, had no effect on the risks associated with nevi. Excluding all subjects with a family history of melanoma did not alter risks associated with dysplastic or other nevi. Trend tests for small, large nondysplastic, and clinically dysplastic nevi were significant with $P<.001$.

Risks associated with clinically dysplastic nevi were substantially higher than those associated with other nevi (Table 3). Individuals with indeterminate lesions were not at increased risk, but those with a single clinically dysplastic nevus showed a 2-fold risk. Risk rose to 12-fold in those with 10 or more dysplastic nevi. Study subjects who currently did not have clinical dysplastic nevi, but who had had dysplastic nevi on previous nevus biopsy specimens, were also at significantly increased risk of melanoma (RR, 14; 95% CI, 7-29). These individuals (n=69) were included in all the models as a separate dysplastic nevus category to avoid misclassification in the referent category because they no longer had clinically dysplastic nevi. Of these study subjects, however, 13% had small nevi with the morphologic characteristics of dysplastic nevi.

After adjustment for other nevi, the number of congenital nevi was not associated with risk (Table 3). There was no significant trend in the risk. On the basis of small numbers (50 cases, 61 controls), the risk of melanoma was not associated with congenital nevi larger than 10 cm; there was no evidence of a gradient in risk with size.

To address the question of risk of melanoma associated with nevi in the absence of dysplastic nevi, we evaluated the patterns of risk with combinations of nevus sizes and counts. In a model that included age, freckling, and large and small nevi, small nevi conferred approximately a 2-fold risk (25-49 small nevi: RR, 1.6; 95% CI, 1.1-2.4; ≥50 small nevi: RR, 2.2; 95% CI, 1.4-3.5) and large nevi conferred a similar risk (1 large nevus: RR, 0.9; 95%

Table 4.—Estimated Relative Risk of Melanoma According to Nevus Categories Among Study Subjects Without Evidence of Dysplastic Nevi or Clinically Atypical Nevi of Any Size

No. of Large Nevi	No. of Small Nevi	No. of Cases	No. of Controls	RR (95% CI)*
0	<25	68	285	1.0 . . .
	25-49	22	40	2.5 (1.4-4.5)
	≥50	11	25	2.1 (1.0-4.6)
1	<25	31	120	1.1 (0.7-1.8)
	25-49	7	28	1.1 (0.5-2.8)
	≥50	7	15	2.1 (0.8-5.6)
2-4	<25	28	77	1.4 (0.8-2.3)
	25-49	14	31	1.9 (0.9-3.7)
	≥50	19	20	3.9 (2.0-8.0)
≥5	<25	9	9	3.8 (1.4-10.0)
	25-49	9	11	3.2 (1.3-8.4)
	≥50	18	17	4.6 (2.2-9.6)

*Relative risk (RR) adjusted for age and freckling. CI indicates confidence interval.

Table 5.—Estimated Relative Risk of Melanoma by Number of Previous Nevus Biopsies and Scars From Nevus Excisions

	No. of Cases	No. of Controls	Adjusted* RR	Adjusted† RR	Adjusted‡ RR (95% CI)
No. of nevus biopsies					
0	499	737	1.0	1.0	1.0 . . .
1	98	147	1.0	0.8	0.5 (0.3-0.8)
2-4	86	95	1.3	0.7	0.4 (0.3-0.7)
5-9	22	14	2.2	1.2	0.4 (0.2-1.2)
≥10	9	5	2.7	1.5	0.8 (0.2-3.3)
No. of scars					
0	582	889	1.0	1.0	1.0 . . .
1	59	63	1.5	1.9	1.7 (1.0-3.0)
2-4	58	40	2.2	2.7	1.9 (1.0-3.8)
≥5	15	6	3.7	2.8	1.4 (0.3-6.0)

*Adjusted for age, sex, center, and referral pattern. RR indicates relative risk.
†Mutually adjusted and adjusted for age, sex, center, and referral pattern.
‡Mutually adjusted and adjusted for age, sex, center, referral pattern, number of dysplastic, small, nondysplastic large, congenital, and morphologic dysplastic nevi smaller than 5 mm. CI indicates confidence interval.

CI, 0.6-1.4; 2-4 large nevi: RR, 1.3; 95% CI, 0.9-1.9; ≥5 large nevi: RR, 2.2; 95% CI, 1.3-3.9). In addition, large numbers of small nevi alone doubled the risk of melanoma (Table 4), but only 14% of the cases and 35% of the controls had only small nevi. Eighty-two percent of controls and 96% of cases with numerous (≥50) small nevi also had large (or clinically dysplastic) nevi. With several large nevi, risk rose to about 4 in the absence of dysplastic nevi. Although risk of melanoma was doubled among subjects without dysplastic nevi who had large nondysplastic nevi, among subjects without large nondysplastic nevi, risk associated with 5 or more clinically dysplastic nevi, adjusted for number of small nevi, age, and freckling, was 5-fold increased (95% CI, 2.0-13.0).

Since both centers have well-known pigmented lesion clinics where patients may have had multiple excisions affecting the current nevus number and type, scars and previous excisions were evaluated. Twenty-six percent of controls and 30% of cases reported previous nevus biopsies, with 11% of controls and 18% of cases having visible scars (Table 5). Most controls reported only 1 biopsy, whereas most cases reported multiple biopsies. Both reported excisions and observed scars were associated with increased risk of melanoma. When adjusted for number and type of nevi, neither factor was associated with melanoma risk. Most of the effect of adjustment for nevi reflected confounding by dysplastic nevi. This suggests that scars seen on physical examination were partly a surrogate for dysplastic nevi once present.

To explore a possible interaction between number of nevi and sun exposure, we evaluated the combined impact of freckling and each of the nevus counts (small, large, and clinically dysplastic). Results for all three were similar; those for clinically dysplastic nevi are shown in Table 6. The freckling index combined degree of freckling on the face, limbs, and upper and lower back; it was the sun-related variable most strongly related to melanoma risk. Among subjects with no clinically dysplastic nevi, those with the most freckling showed a 3-fold risk of melanoma (Table 6). Among subjects with little or no freckling, those with numerous dysplastic nevi showed at least a 10-fold risk of melanoma. Individuals with the most dysplastic nevi who were heavily freckled were at the highest risk (RR, 20), but these risks were not significantly different from those in subjects with many dysplastic nevi and few freckles.

The RRs of melanoma associated with the numbers of small, large, or clinically dysplastic nevi were similar in men and women and in San Francisco and Philadelphia (eg, for ≥10 dysplastic nevi, RR was 12 for men, 11 for women, 11 in San Francisco, and 11 in Philadelphia). Relative risks associated with the number of small nevi were slightly higher among subjects younger than 50 years than in those older than 50 years, and risks for large nevi were slightly higher among older subjects, but not significantly different. The risks associated with multiple dysplastic nevi were somewhat higher in the older age group (2-4 dysplastic nevi: RR, 9.1; 95% CI, 4.2-20; 5-9 dysplastic nevi: RR, 3.1; 95% CI, 1.1-9.1; ≥10 dysplastic nevi: RR, ∞) than in the younger (2-4 dysplastic nevi: RR, 5.3; 95% CI, 3.1-9.2; 5-9 dysplastic nevi: RR, 4.9; 95% CI, 2.1-11; ≥10 dysplastic nevi: RR, 6.8; 95% CI, 2.6-18). All 14 subjects older than 50 years with 10 or more dysplastic nevi had melanoma. Among the controls, 21% of those younger than 50 years had 50 or more small nevi and 15% had dysplastic nevi, whereas 10% of the controls aged 50 years or older had 50 or more nevi and 7% had dysplastic nevi.

COMMENT

According to Foulds[24] and Clark,[25] tumor progression consists of a series of qualitatively different proliferative lesions that compose a neoplastic system. Few, if any, precursor lesions progress to cancer. Examples of such neoplastic systems include differing types of colonic polyps with progressive genetic variation and colon carcinoma[26,27]; cervical atypia, dysplasia, and carcinoma[28,29]; and differing kinds of melanocytic nevi and melanoma.[21,30,31] Various antigenic studies and analyses of molecular components of melanocytic lesions that may lead to melanoma have consistently shown dysplastic nevi to be intermediate between other nevi and melanoma.[32,33] The present study, although cross-sectional, illustrates again the significance of the different sequential lesions from which melanoma is formed. Risk of melanoma rose with increasing number and clinical atypia of nevi from small risks in those with few small nondysplastic nevi, to slightly higher risks with larger nondysplastic, to very high risks in those with multiple clinically

dysplastic nevi. Other investigations have not had sufficient study subjects to clearly separate risks associated with dysplastic nevi from those without dysplastic nevi. These data demonstrate the difficulty in this separation. Among the 292 cases with 50 or more small nevi, only 19% had no evidence of dysplastic nevi, compared with 51% of the controls with 50 or more nevi.

The level of risk associated with dysplastic nevi and the percentage of melanoma cases with dysplastic nevi imply that dysplastic nevi are the central risk factor for cutaneous melanoma. Approximately half of the melanoma cases had dysplastic nevi, similar to reports by others.[9-11,17,34] Of note, even 1 unequivocal clinically dysplastic nevus conferred a significant risk. Clinically dysplastic nevi confer substantially higher RRs of melanoma than do other types of nevi, including congenital nevi. These elevated risks are consistent with dysplastic nevi being an intermediate end point in melanoma development. Even though clinically dysplastic nevi were in part defined by size, small nevi with similar morphologic characteristics also conferred increased risk. The size criterion was included to minimize interobserver variability.[35] Although the risk associated with nondysplastic nevi is significantly lower and present in a smaller proportion of the cases, these nevi do appear to confer modest risk of melanoma independent of clinical atypia. This implies a separate pathway in melanoma etiology.

On the basis of the number and type of nevi, a clinician can assess risk of melanoma. Individuals with no large but numerous small nevi have a doubled risk of melanoma. If they also have multiple large nondysplastic nevi, the risk rises to approximately 4-fold, while the presence of multiple dysplastic nevi confers a 10-fold risk.

In this study and in clinical practice, the number of nevi seen at the time of examination reflects only those not excised or not regressed. Sixty-nine subjects (cases and controls) had had previous biopsy specimens diagnostic of dysplastic nevi on histologic review but had no remaining dysplastic nevi at the time of examination. In other studies, they would have been included with the study subjects without dysplastic nevi, because few previous studies have evaluated scars and previous biopsies. The observation that scars are partly a surrogate for dysplastic nevi suggests that multiple nevus biopsy scars may be a clinical clue that an individual may previously have had more abnormal or dysplastic nevi. Histologic dysplasia appears important in risk of melanoma; the significance of histologic diagnoses by means of strict criteria needs further exploration.[36]

Table 6.—Estimated Relative Risk of Melanoma by Number of Dysplastic Nevi and Freckling Index*

	No. of Clinically Dysplastic Nevi				
Freckles	None	Indeterminate	1	2-4	≥5
None					
RR	1.0	1.8	2.9	24	15
95% CI	. . .	0.5-7.0	0.7-12	3.5-163	2.0-106
Cases:controls	21:102	3:8	3:5	5:1	3:1
Few					
RR	1.4	2.6	4.6	11	27
95% CI	0.8-2.3	1.4-5.0	2.2-9.8	5.1-21	11-67
Case:controls	117:409	32:59	22:23	41:19	39:7
Moderate					
RR	2.9	5.6	9.4	26	22
95% CI	1.7-4.9	2.8-11	4.3-20	11-58	9.4-52
Cases:controls	122:202	32:28	29:15	53:10	41:9
Many					
RR	3.1	1.4	6.9	36	21
95% CI	1.7-5.6	0.4-5.4	2.4-20	10-121	6.8-64
Cases:controls	41:65	3:10	10:7	22:3	17:4

*RR indicates relative risk; and CI, confidence interval.

Previous evaluations of the role of dysplastic or clinically atypical nevi in the etiology of melanoma have been criticized because of alleged lack of specificity and reproducibility of clinical diagnoses of dysplastic nevi. To address this issue, we included review of photographed lesions as a further validation procedure. This review demonstrated that clinical diagnoses are reproducible among experienced examiners.[20] All diagnoses in this study were reviewed by experienced clinicians. When there was a questionable diagnosis of clinically dysplastic nevi, subjects were classified in a separate category. As would be expected in a diagnostic continuum from normal to abnormal, questionable lesions were associated with a risk intermediate between completely normal and clearly dysplastic. We also attempted to account for all previous nevus biopsies to minimize misclassification, since some individuals with multiple atypical lesions may have had many or all of them removed.

Most of the adjustment in risk in the multivariate analyses resulted from mutual adjustment for nevi. Adding other variables that are important for melanoma risk in univariate analyses, such as sun exposure factors, previous nevus biopsies, number of scars, and family history of melanoma, had little additional effect on the risks.

There remains a substantial proportion of melanomas that do not arise in the setting of dysplastic nevi. Among individuals with these melanomas, there appears to be a consistent, modestly elevated risk associated with other types of nevi and with freckling. Both clinical variables may be surrogates for past sun exposure, particularly since risks of nevi decreased somewhat with adjustment for freckling and sunburns. Freckling reflects both host susceptibility and sun exposure and increases melanoma risk even after accounting for the effects of nevi. Freckling also is easily quantifiable by clinicians during the clinical examination and is less subject to recall bias than sun exposure history. In these data, risks associated with freckling roughly added to (rather than multiplied) risks associated with all types of nevi. These observations are consistent with the view that melanoma is a complex disease with multiple etiologic pathways, as demonstrated by genetic heterogeneity in melanoma-prone families.[37-39]

The finding of stronger association of melanoma risk with nevus number in subjects older than 50 years is particularly interesting, given the natural course of nevi.[40-42] Nevus numbers peak in young adulthood. By age 50 years, nevi tend to decrease in number, but persistent large numbers of nevi are seen in individuals older than 50 years with dysplastic nevi. Even dysplastic nevi tend to differentiate or disappear over time,[43] and the finding of dysplastic nevi in older individuals may mark subjects at particularly increased risk of melanoma.

The effects of nevi were similar in both geographic locations. Since this study was clinic based, it cannot represent the general population. Indeed, the prevalence of dysplastic nevi in the control group was somewhat higher than that in population-based surveys in other countries[17,44] but similar to that in other clinic-based studies.[9,16] This may reflect a true difference between our subjects and the general population, or response bias in the control group. The latter is possible, since people with skin lesions

may have been more willing to undergo extensive examinations and interviews than were eligible controls who declined participation (eg, 26% of controls also reported at least 1 nevus biopsy in the past). Such response bias would tend to reduce the difference between case and control groups and lower the RRs. Thus, the strong relationships of number of nevi to melanoma risk may be underestimated.

Although controversy remains regarding nomenclature, specific clinical attributes, and histologic diagnosis of dysplastic nevi, these lesions are a major determinant of melanoma risk and are central in the identification of high-risk individuals. On the basis of clinical examination attributes alone, a clinician can estimate the risk of melanoma. Once high-risk individuals are identified, screening and prevention programs can be rationally designed for prevention and early detection of this epidemic cancer.

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